TABLE I.—PARTICLE SIZE OF PREPARED PROGESTERONE CRYSTALS[a]

Insonation Time / Plate Power, ma.	5 sec. Arithmetic Mean, μ	5 sec. S.D.	15 sec. Arithmetic Mean, μ	15 sec. S.D.	25 sec. Arithmetic Mean, μ	25 sec. S.D.
50	47.3	9.4	23.7	12.2	18.6	9.4
75	16.9	7.5	9.3	4.4	13.5	4.9
100	11.0	3.3	7.8	4.4	8.8	4.1
125	16.9	4.7	9.5	4.5	9.9	4.5
150	14.5	7.1	10.2	8.2	7.3	3.1

[a] Solvent, ethyl alcohol U.S.P., 25 parts, ethylene glycol, 75 parts; insonation time, 5 seconds; saturated solution prepared at 55°.

Figure 1 shows crystals obtained under the conditions specified in Table I, at a plate power of 50 ma. and 5 seconds exposure time. Figure 2 shows crystals exposed for 5 seconds at a plate power of 100 ma.

SUMMARY

1. Microscopic crystals of progesterone were prepared by insonating saturated solutions of the hormone.

2. The results indicated that: (*a*) in general, an increase in plate power from 50 to 100 ma. results in smaller crystals; (*b*) the solvent system 25% ethyl alcohol–75% ethylene glycol appears to favor smaller and more uniform crystal size; (c) the temperature at which the saturated solution is prepared seems to affect crystal size; (*d*) length of time of insonation appears to have minimal influence on crystal size.

3. Crystals prepared under insonation conditions were smaller and more uniform than controls prepared without insonation.

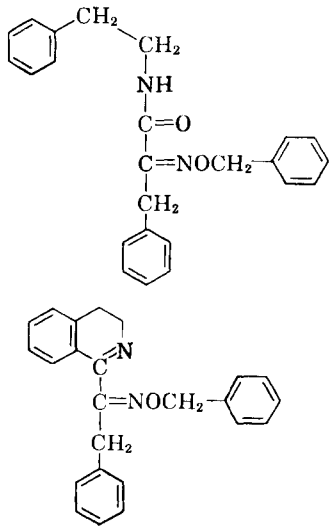
Amides of α-Alkyloximino Acids

By WALTER H. HARTUNG† and DOMINICK A. COVIELLO‡

N-β-Phenethyl amides of α-benzyloximino acids were prepared as intermediates for an attempted cyclization to the corresponding 3,4-dihydroisoquinoline derivatives.

THE ISOQUINOLINE nucleus is found in a large number of medicinally active compounds, both natural and synthetic. With this and the fact that little is known about the biological activity of the alkyloximino group in mind, it was thought that if a substituent containing the alkyloximino group could be introduced into the isoquinoline nucleus a compound of biological interest might result. At the same time, there was also the opportunity to explore further the chemical stability and limitations of the group under various conditions of reaction.

The plan was to prepare N-β-phenethyl amides of α-benzyloximinopropionic acids with the hope that they could be cyclized under the conditions of the Bischler-Napieralski reaction (1) to obtain new 3,4-dihydroisoquinoline derivatives containing the alkyloximino group. These presumably could be dehydrogenated to yield isoquinolines. For example, N-β-phenethyl-β-phenyl-α-benzyloximinopropionamide would yield 1-(1-benzyloximino-2-phenylethyl) 3,4-dihydroisoquinoline.



The amides prepared in this investigation are listed in Table I.

Cyclization was attempted by refluxing the amides

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TABLE I.—AMIDES PREPARED

Amide	M.P., °C.	Yield Based on Amine, %	Kjeldahl Nitrogen Calcd., %	Kjeldahl Nitrogen Found, %
N-β-Phenethyl-β-phenyl-α-benzyloximinopropionamide	54–56	55.3	7.53	7.52[a] 7.54
N-β-(3,4-Dimethoxyphenethyl)-β-phenyl-α-benzyloximinopropionamide	46–48	40.3	6.48	6.47 6.35
N-β-(3,4-Methylenedioxyphenylethyl)-β-phenyl-α-benzyloximinopropionamide	53–54	33.7	6.71	6.67 6.52
N-β-Phenethyl-α-benzyloximinopropionamide	41–43	[b]	9.49	9.38 9.22

[a] *Anal.*—Calcd. for $C_{24}H_{24}N_2O_2$: C, 77.4; H, 6.45; N, 7.53. Found: C, 77.3, 77.4; H, 6.24, 6.33; N, 7.3. Analyses done by Drs. Weiler and Strauss, Oxford, England. [b] No yield was calculated on this compound because an attempt was made to distil a portion since it showed no inclination to crystallize by the usual methods. The remaining portion, standing at room temperature for several weeks, crystallized. The portion which distilled at 184–195°/0.2 mm. did not crystallize even after standing for several months.

in toluene in the presence of phosphorus oxychloride and phosphorus pentoxide. The experiment was repeated with *p*-xylene solvent and without solvent. In another experiment, the amide was allowed to stand at room temperature for one week in phosphorus oxychloride. Another experiment at room temperature employed phosphorus pentoxide with the phosphorus oxychloride. In no case was a product isolated which had amine properties.

In light of this, an attempt was made to effect cyclization with polyphosphoric acid according to the procedure of Snyder and Werber (2). By this method the amine moiety was recovered and characterized as the picrate. From this it was assumed that the unchanged amide was hydrolyzed during decomposition of the hot reagent with ice. This was borne out by the fact that if the reaction mixture was allowed to cool before decomposition of the reagent, nothing could be isolated that had amine properties.

Experiments using polyphosphoric acid were run varying reaction time from 30 seconds to one and one-half hours at temperatures ranging from 50 to 145°, and at room temperature for one week without success.

EXPERIMENTAL

Amides were best prepared by the procedure of Vaughan and Osato (3). The products appeared at first to be intractable oils, but a pure product was ultimately obtained by taking up the oil in methanol and adding hexane until precipitation was imminent. After 2 days to a week in the freezing compartment of the refrigerator, a solid formed which was crystallized from methanol.

REFERENCES

(1) Bischler, A., and Napieralski, B., *Ber.*, **26**, 1903(1893).
(2) Snyder, H. R., and Werber, F. X., *J. Am. Chem. Soc.*, **72**, 2962(1950).
(3) Vaughan, J. R., Jr., and Osato, R. L., *ibid.*, **73**, 5553 (1951).

Use of an Approximate Dielectric Constant in Solubility Studies

By WILLIS E. MOORE

THE DATA published by Autian and Udani (1) on the solubility of secobarbital have been further evaluated in terms of solubility in relation to the approximate dielectric constant (A.D.C.) of the solvent(s) by the techniques proposed by Moore (2).

This additional analysis is noted here to further illustrate the utility of using an A.D.C. in solubility studies.

The binary systems in Autian and Udani's work (their Fig. 2) were examined. Only glycerin showed a linear relationship between A.D.C. and solubility [log A.D.C. was plotted *vs.* (concentration)$^{1/2}$ of solute]. Alcohol, propylene glycol, and PEG 400 showed varying degrees of positive deviation.

The ternary systems (their Fig. 3) show linear portions in all three systems when plotted as above. The slopes differed, since solubility was different, but the intercepts were identical at a log A.D.C. value equal to an A.D.C. of 88 (see Fig. 1). This predicts a zero solubility of secobarbital in a mixed solvent with an A.D.C. of 88. This value could, of course, be meaningless. Further investigation of this relationship is required for better understanding.

Figure 1 further shows that an inconsistency appears. For example, at an A.D.C. value of 59.5 (log A.D.C. = 1.775) the solubilities of secobarbital are predicted as in Table I.

Why the solubility should vary at a constant A.D.C. but with different solvent systems cannot be explained precisely by this empirically established relationship. It is recognized that the dielectric

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